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Review of detection frequency and type of synthetic cannabinoids in herbal compounds analyzed by Istanbul Narcotic Department of the Council of Forensic Medicine, Turkey☆

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ABSTRACT

In recent years, synthetic cannabinoids have been frequently observed in seized materials all over the world. This new generation of designer drugs, mixed with herbal substances, is also known as “Herbal Highs” or “Legal Highs”.

There are many articles about the history, type and pharmaco-chemical properties of synthetic cannabinoids in the literature; however the number of articles about the frequency of their detection is limited. In this study, we evaluated the type and detection frequency of synthetic cannabinoids in Istanbul and its surrounding area. The reports of the Council of Forensic Medicine-Istanbul Narcotic Department were retrospectively reviewed for the presence of synthetic cannabinoids in herbal compounds sent by the judicial authorities between August 01, 2010 and March 31, 2012. Among 1200 herbal compounds, 1179 of them (98.3%) contained synthetic cannabinoids. Twenty-one samples (1.7%) had other psychoactive substances. The analysis of 1179 samples showed that JWH-018 was present in 1172 (99.4%) of the samples. JWH-081 was found in 777 samples (65.9%) together with JWH-018. Samples had different package names. “Bonzai Aromatic Potpourri” (n = 755; 64.0%) and “Bonzai Plant Growth Regulator” (n = 316; 26.8%) were the most common product names amongst the herbal products in this study. It is clear from the present study and previous studies that brand name of synthetic cannabinoids that dominate the market exhibit regional differences as to the type and detection frequency of synthetic cannabinoids and the content of herbal highs packages.

The number and diversity of synthetic cannabinoid compounds have increased dramatically in the drug market in recent years. New, different, potent derivatives appear on the market almost every day and this presents important problems that need to be solved by scientists and judicial authorities working to prevent their harm. These problems include the limited knowledge about their frequency, the

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lack of analytical data and reference standards for analysis of these new derivates, the lack of information on their toxic effects, and information about the metabolism and metabolites for toxicological analysis in human subjects.

1. Introduction

Cannabinoids are a diverse group of substances acting on cannabinoid receptors CB1 and CB2 and produce a wide range of responses throughout the body. They are classified mainly in three groups: natural cannabinoids, endogenous cannabinoids and synthetic cannabinoids. The most well-known example of natural cannabinoids is delta9-tetrahydrocannabinol (THC), the main active ingredient of marijuana.[1] Endogenous cannabinoids include 2-arachidonoylglycerol and anandamide. The third group, synthetic cannabinoids, consists of the molecules created in laboratories (scientific or clandestine) to mimic the effects of THC.[2,3]

The first record about marijuana (*Cannabis sativa*) which dates back over 10,000 years to the Stone Age was found in Taiwan.[4] Its medical use dates back over 5000 years, in the ancient inscription and folklore of India and China.[4–6] It was reported that, in 2737 B.C., the Chinese Emperor Shen Nung (Chen Nung) discovered marijuana's healing properties and he wrote a monograph about the use of cannabis in treating several diseases including migraine, asthma and some gynaecological disorders.[4,6] Marijuana continued to be used for medical purposes throughout the centuries in near and far eastern countries. In 1842, Dr W.B. O Shaugnessy, an army surgeon in India, introduced an extensive treatise about medical use (as analgesic, antispasmodic and anticonvulsant) of cannabis to the British medical community.[5,6] In the following years, cannabis became widely used in Britain and the United States as a part of medical treatment until the beginning of the 20th century.[4–6]

As a result of long researches aiming at more effective therapeutic uses of cannabis, the first analogues of THC were reported in the early 1940s.[7] After the 1960s, following the isolation of THC as the main active substance in *C. sativa*, new cannabinoid receptor agonists such as HU-210 (100 times more potent than THC), Nabilone, Dronabinol were synthesized and the number of THC analogues increased rapidly.[8–10] In 1970s, the cyclohexylphenol (CP) series, which included CP-59,540, CP-47,497 and their n-alkyl homologues were created, and in the years following, up to 1994, most of naphthoylindoles and their homologues (including JWH-015, JWH-018, JWH-073, JWH-398), naphthylmethylindoles, naphthoylpyrroles, naphthylmethylindenes and phenylacetylindoles (include JWH-250) were developed.[10]

Synthetic cannabinoids have been classified according to their chemical structures by Howlett et al.[11] This classification was referred, as shown below, in the report on synthetic cannabinoids found in herbal products produced by the United Nations Office on Drugs and Crime (UNODC)[12]:

1. Classical cannabinoids (THC, other constituents of cannabis and their structurally related synthetic analogues, e. g. HU-210, AM-906, AM-411, O-1184)
2. Nonclassical cannabinoids (cyclohexylphenols or 3-arylcyclohexanols such as CP-47,497-C8, CP-55,940, CP-55,244)
3. Hybrid cannabinoids (combinations of structural features of classical and non-classical cannabinoids, e. g. AM-4030)
4. Aminoalkylindoles (AAIs), which can be further divided into naphtoylindoles (e. g. JWH-018, JWH-073, JWH-398, JWH-015, JWH-122, JWH-210, JWH-081, JWH-200, WIN-55,212); phenylacetylindoles (e. g. JWH-250, JWH-251); naphthylmethylindoles and benzoylindoles (e. g. pravadoline, AM-694, RSC-4).
5. Eicosanoids (endocannabinoids such as anandamide, and their synthetic analogs, e.g. methanandamide)
6. Others, diarylpyrazoles (selective CB1 antagonist Rimonabant®), naphtoylpyrroles (JWH-307), naphthylmethylindenes or derivatives of naphthalene-1-yl- (4-pentyloxynaphthalen-1-yl) methanone (CRA-13)

In contrast to this, the British Advisory Council on the Misuse of Drugs (ACMD) classified synthetic cannabinoids in seven groups based on their chemical structure and accordingly suggested a "generic definition" in the legal control of these substances.[13] These included: 1-Naphthoylindoles (e.g. JWH-018, JWH-073, JWH-081); 2-Naphthylmethylindoles (e.g. JWH-185, JWH-199); 3-Naphthoylpyrroles (e.g. JWH-369, JWH-370); 4-Naphthylmethylindenes (e.g. JWH-176); 5-Phenylacetylindoles (benzoylindoles: e.g. JWH-250); 6-Cyclohexylphenols (e.g. CP 47,497 and its homologues); 7-Classical cannabinoids (dibenzopyrans: e.g. THC, HU-210).

In recent years, synthetic cannabinoids have frequently been observed in seized materials all over the world. This new generation of designer drugs, which are mixed with herbal substances in sold materials, is also known as "Herbal Highs" or "Legal Highs".[14] According to previous reports, these products, which were named as "herbal incense products", can easily be obtained via the internet and from some specialized shops such as gas stations, convenience stores, and head shops without age restrictions,[9,10,14–16] with different brand names, including : Spice, Spice Silver, Spice Gold, Spice Diamond, Spice Arctic Synergy, Spice Tropical Synergy, Spice Egypt, K2, Mojo, Aroma, Dream, Chill X, Chaos, Sence, Smoke, Skunk, Silent, Black, Genie, Algerian Blend, Yucatan Fire, Tai, Fun, Sensation, SpicyXXX, Spike 99, Bonsai-18, Banana Cream Nuke, Wicked X, Natures, Organic, Zen, Spice Gold, Silver, Scene, Ex-ses, Spark, Blaze, Highdi's Almdröhner, Earth Impact, Gorillaz, Genie, Galaxy Gold, Space Truckin, Solar Flare, Moon Rocks, Blue Lotus, Scope, Dream, etc.[9,17–19]

Although there are many articles about the history, type and pharmaco-chemical properties of synthetic cannabinoids in the literature, the number of articles about the frequency of their detection is limited.

In this study, we evaluated the type and detection frequency of synthetic cannabinoids in Istanbul and its surrounding area.

2. Material and methods

The reports of herbal compounds that were analyzed between August 01, 2010 and March 31, 2012 in the Istanbul Narcotic Department of the Council of Forensic Medicine at the request of the judicial authorities were retrospectively reviewed for synthetic cannabinoids. The reports about classical marijuana were not included in the study.

The results were statistically evaluated by the Chi-square test. The level of significance was $p \leq 0.05$.

3. Results

A total of 1200 herbal compounds (except classical marijuana) were reported during a 20-month study period and 1179 of them (98.3%) contained synthetic cannabinoids. The total weight of analyzed herbal compounds was 11786.47 g and of these

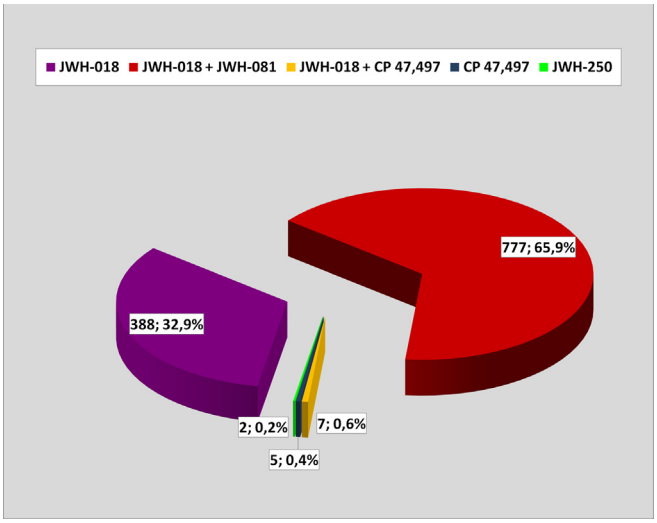

Fig. 1. The number of samples containing different types of synthetic cannabinoids.

3496.14 g (29.7%) showed the presence of synthetic cannabinoids. In the remaining herbal compounds (1.8%, in total 8290.33 g), other psychoactive components were detected: Methylenedioxypyrovalerone (MDPV) (totally 15 samples and 5.93 g), MDPV and Mephedrone (4-MMC) (totally 1 sample and 1 g), Divinorin A (totally 2 samples and 2 g), and mix of cathinone and cathine (totally 3 samples and 8281.4 g). In the analysis of 1179 samples containing synthetic cannabinoids, JWH-018 was found in 1172 samples (99.4%) and JWH-081 together with JWH-018 in 777 samples (65.9%) (Fig. 1).

Herbal compounds containing synthetic cannabinoids had different package names such as "Bonzai Aromatic Potpourri" ($n = 755$; 64%), "Bonzai Plant Growth Regulator" ($n = 316$; 26.8%), "Jamaican Gold" ($n = 46$; 3.9%), "Heaven" ($n = 14$; 1.2%), "Yukatan Fire" ($n = 7$; 0.6%), "Smoke XXX" ($n = 6$; 0.5%), "Aromatic Incense", ($n = 6$; 0.5%), "Jamaican Sprit" ($n = 5$; 0.4%), "Tribal Warrior Ultimate" ($n = 5$; 0.4%), "Bonzai Cuba" ($n = 4$; 0.3%), "Bonzai Black Diamond" ($n = 3$; 0.3%), "Jamaican Gold Extreme" ($n = 1$; 0.1%), "Dragon Herbal Incense" ($n = 1$; 0.1%) and "Ivory Wave" ($n = 1$; 0.1%) (Fig. 2). Nine samples (0.8%) were not in the original package. Four samples were sent in unnamed aluminum packages, 3 samples between the pages of a magazine, 1 sample in a piece of gelatin and 1 sample in an evidence package collected from the crime scene.

The contents of each package are shown in detail in Table 1. The weights of packages were mostly 3 g.

4. Discussion

Smokable herbal mixtures called 'Spice' and "K2" were firstly sold online in 2004 according to data obtained from web forums and Google Insight web searches, in several European countries such as Germany, Switzerland and Great Britain.[9,12,16,20] It was reported that "initially, these products were not popular and were used by only a small group of experimental users".[12] However these products were offered for sale under the labels "incense", "exotic incense blends with a rich aroma", "for aromatherapy use only" and "not for human consumption".[9,16] In 2008 in Germany, some news

Fig. 2. Appearance of some investigated packages.

Table 1
The content of each sample which includes synthetic cannabinoids.

Product name	Number of packages ($n = 1156$)	Total weights of products (g)	Weights of each product (g)	Type of synthetic cannabinoids				
				JWH-018	JWH-081	JWH-250	CP47,497(C8)	RCS-4
Bonzaı aromatic potpourri	755	2292.00		+	+			
Bonzaı plant growth regulator	316	935.06	306 × 3.00 7 × 2.40 1 × 0.24[f] 2 × 0.01[e]	+	[a]	[b]		
Jamaican gold	46	135.01	45 × 3.00 1 × 0.01[e]	+				[c]
Heaven	14	36.80	13 × 2.60 1 × 3.00	+				
Yucatan fire	7	14.00	7 × 2.00	+			+	
Smoke XXX	6	20.40	6 × 3.40	+				
Aromatic incense	6	3.00	6 × 0.50	+				
Jamaican spirit	5	14.00	5 × 2.80	+	+			
Tribal warrior ultimate	5	15.00	5 × 3.00				+	
Bonzai cuba	4	8.00	4 × 2.00	+				
Bonzai black diamond	3	6.00	3 × 2.00	+				
Jamaican gold extreme	1	1.70	1 × 1.70	+	+			
Dragon herbal incense	1	3.00	1 × 3.00	+				
Ivory wave	1	2.80	1 × 2.80	+				
Unnamed packages[d]	9	9.37	1 × 2.40 3 × 2.30 1 × 0.03[e] 4 × 0.01[e]	+	+			

[a] JWH-081 along with JWH-018 was detected in 7 packages.
[b] Only JWH-250 was detected in 2 packages.
[c] In 1 package, RCS-4 was detected along with JWH-018.
[d] In 4 aluminum packages, MDPV was detected along with JWH-018 and JWH-081.
[e] Packages contaminated with substances.
[f] Partly used package.

and articles claimed that use of these products instead of cannabis was “legal”. It was reported that this kind of information raised their popularity and the number of users of “Spice products” increased dramatically in the course of the year.[12,21] The promise of a more intense high than cannabis, affordability, easy access, and avoidance of detection in standardized drug tests likely contributes to the growing use of Spice.[16,18] During the same period, this incursion was observed in Italy, France, Norway, Finland and many other European countries, as well.[9,12,20,21] According to the United States reports, the initial appearance of synthetic cannabinoids in herbal incense products was in November of 2008, and an excess of 500 exhibits containing synthetic cannabinoids was reported in the 9 months between January 2010 and September 2010.[22] Whilst the number of calls concerning synthetic cannabinoids made to the American Association of Poison Control Centers was 14 in 2009, the number of calls increased to 2915 in 2010 and 5741 in 2011 as of October 31.[23,24]

In Turkey, the first capture of a synthetic cannabinoid (JWH-018) by the police departments was in May 2010.[25] Initial samples were sent to be analyzed to the laboratory of the Istanbul Narcotic Department of the Council of Forensic Medicine in August of 2010. In the present study it was found that, the majority ($n = 1179$; 98.3%) of 1200 herbal compounds, sent by judicial authorities to The Council of Forensic Medicine-Istanbul Narcotic Department between August 01, 2010 and March 31, 2012, contained synthetic cannabinoids ($p \leq 0.05$). Although the number of other psychoactive components ($n = 21$) was smaller than that of synthetic cannabinoids, their total weight (8290.33 g) was higher than the weight of herbal material containing synthetic cannabinoids (totally 3496.14 g) ($p \leq 0.05$).

In an investigation done in Italy, it was reported that there was JWH-018 in 10 (52.6%) out of 19 samples (which was associated with JWH-073 in 1 sample) and with JWH-122 in 9 (47.4%) samples (which associated with JWH-250 in 3 samples).[26]

In a study from the United States, it was reported that; the abuse of designer drugs has increased greatly. In 2011, about 1 out of every 4 samples (73%) tested for the designer drug synthetic cannabinoids was positive and use of at least JWH-073 was detected in nearly 97% of urine samples positive for synthetic cannabinoids. Frequencies of other synthetic cannabinoids were described to be 49% for JWH-018, 31% for JWH-019 and 8% for JWH-250.[27]

In another study from the United States, it was described that, JWH-018 was present in 40–60% of the blood samples examined each month and JWH-073 was present in 10–20% of the blood samples examined each month until March 2011. In March 2011, as a result of banning of five chemicals including JWH-018 and JWH-073, the positivity rates of JWH-018 and JWH-073 in blood specimens dropped drastically. Unfortunately, drug users continued to use other chemicals including AM-2201, JWH-122 and JWH-210 that are not controlled and these have become more widely used. Approximately 32% of urine samples submitted for synthetic cannabinoid testing at the National Medical Services (NMS) Labs in the United States during the period between September 2011 and December 2011 were positive for one or more synthetic cannabinoids. Despite lower positivity rates of JWH-018 and JWH-073 in the blood samples, their positivity rates in urine samples were found to be higher. In December 2011, the positivity rates of synthetic cannabinoid metabolites in urine were ~31% for JWH-018, ~17% for AM2201, ~13% for JWH-073, ~5% for JWH-250, ~4% for JWH-019 of the samples tested.[28]

According to the Health Care Provider Fact Sheet of the Bureau of Disease Control, Michigan Department of Community Health (Prevention & Epidemiology and Children’s Hospital of Michigan Poison Control Center) the use of synthetic cannabinoids and the number of users of synthetic cannabinoids rose to 6995 in the United States and 224 in Michigan in 2011, whereas the numbers had been 2906 in the United States and 17 in Michigan in 2010. By the end of February 2012, the number in Michigan was 85.[29]

According to an Italian study, the products containing synthetic cannabinoid were: "n-joy" ($n = 6$; 31.6%), "Jungle Mystic Incense" ($n = 5$, 26.3%), "Forest Green" ($n = 3$; 15.8%), "Bonzai" ($n = 3$; 15.7%) and "Spice Arctic Synergy" ($n = 1$; 5.3%) "Orange Alesya New" ($n = 1$; 5.3%).[26]

In Michigan the most frequently confronted brand names on packages of synthetic cannabinoids were: "K2", "Spice", "Genie", "Devil's Wrath", "Yucatan Fire", "King Krypto", "Mr. Nice Guy", "K-3", "Red Magic", "Blueberry Medication", "Super Skunk", "Black Mamba", "Bliss", "Bombay Blue", and "Zohai".[29]

Bonzai Aromatic Potpourri" ($n = 755$; 64%) and "Bonzai Plant Growth Regulator" ($n = 316$; 26.8%) were the most common product names amongst the herbal products reported in this study ($p \leq 0.05$) (Table 1).

In a study performed in Italy by Gattardo et al., packages that included synthetic cannabinoids were investigated. They reported that JWH-018 was present in "Afghan Incense", "Bonzai", "Jamaican Gold", "Mojo" and "Orange Lilia"; JWH-250 in "Amazonas", "Bonzai Citrus" and "Ketama Gold"; JWH-018 + JWH-250 in "Jamaican Sprit"; JWH-073 in "Infinity "and "Orange Oxana"; and JWH-018 + JWH-073 in "N'Joy" packages.[30] Hudson et al. reported that there were different synthetic cannabinoids in different packages with the same brand name.[31]

In our study, JWH-018 was the most frequent type ($n = 1172$; 99.4%) of synthetic cannabinoids within 1179 samples. The other synthetic cannabinoids were JWH-081 ($n = 777$; 65.9%); CP 47,497 ($n = 12$; 1%) and JWH-250 ($n = 2$; 0.2%) ($p \leq 0.05$) (Fig. 1). All "Yucatan Fire" packages ($n = 7$) contained JWH-018 with CP 47,497 (C8). "Tribal Warrior Ultimate" packages ($n = 5$) had CP 47,497(C8). "Bonzai Aromatic Potpourri" packages ($n = 755$), "Jamaican Gold Extreme" package ($n = 1$) and unnamed packages ($n = 9$) had JWH-018 with JWH-081. Four of the unnamed packages also had MDPV. Of the "Bonzai Plant Growth Regulator" packages ($n = 316$), 7 had JWH-081 along with JWH-018, 2 had JWH-250, others ($n = 307$) had JWH-018. One of the "Jamaican Gold" packages ($n = 46$) had RCS-4, others ($n = 45$) had JWH-018. The rest of packages with different names had JWH-018 (Table 1).

It is clear from the present study and previous studies that brand name of synthetic cannabinoids that dominate the market exhibit regional differences as to the type and detection frequency of synthetic cannabinoids and the content of herbal highs packages.

Nowadays, in many countries, synthetic cannabinoid compounds and their analogues have been banned by law or juridical studies have been initiated for prohibition.[32]

In Turkey, some of these synthetic cannabinoid compounds (JWH-018, CP 47, 497, JWH-073, HU-210, JWH-200, JWH-250, JWH-398, JWH-081, JWH-073 methyl derivate, JWH-015, JWH-122, JWH-203, JWH-210, JWH-019), some of Phenethylamine group substances (2C-B, 2C-P), Cathinone, Cathine and the plant named Catha Edulis have been banned by law.[33] However, there has not been a clause relating to an "analogue or derivative of them" established in the law yet.

Although they did not evaluate in this study, the synthetic cathinones, commonly called "bath salts; Kratom, a plant product derived from *Mitragyna speciosa* Korth; *Salvia divinorum* as a hallucinogen; Methoxetamine which is marked as "legal ketamine"; the piperazine derivatives, a class of amphetamine-like compounds that includes BZP and TMFPP, are making a resurgence as "legal Ecstasy" are available via the Internet, frequently legal, and often perceived as safe by the public.[34]

Seeley et al. reported that, "since most synthetic cannabinoids are not currently found using routine toxicology screening tests, health care providers, especially those working in emergency care settings, should be constantly on alert for Spice-induced toxicity despite negative drug-screening results. Limited data are currently available on the pharmacodynamics and pharmacokinetics of synthetic cannabinoids. The wide abuse of Spice highlights the urgent need for further evaluating the synthetic cannabinoids effects in vivo to[1]: improve our understanding of how these compounds interact with cannabinoid and non-cannabinoid receptors in both the brain and periphery,[2] better characterize the pharmacology and toxicology,[3] properly delineate drug scheduling and legislation,[4] develop treatments for intoxication, and[5] implement effective deterrents like workplace and athletic monitoring programs".[16]

5. Conclusion

The number and diversity of synthetic cannabinoid compounds on drug market has increased dramatically in recent years. These so called "herbal highs", which have undeclared chemical substances many times stronger than natural cannabis, pose a significant threat for human health and public health through their toxic effects. Furthermore, the appearance of new synthetic cannabinoids on the illicit market is a challenge for clinical laboratories and forensic toxicologists because there is lack of reference standards and analytic methods for law enforcement and judicial authorities because these are inadequate and one step behind law.

We hope that scientists who are experienced in crime prevention and police departments that are internationally well organized against crime organizations will fully cope with the public harm of synthetic cannabinoid compounds as soon as possible.

Ethical approval

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Conflict of interest

None.

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